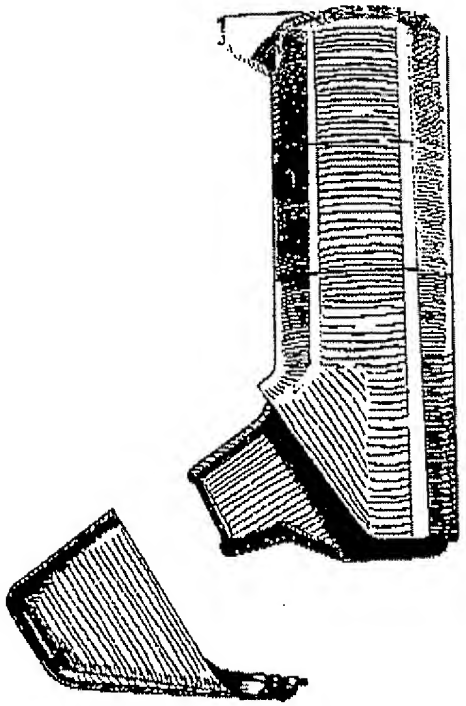
A New Millennium for Inhaler Technology

Anthony J. Hickey* and Craig A. Dunbar



In recent years dramatic developments have occurred in the technology associated with aerosol delivery of drugs to the lungs. Propellant-based metered-dose inhalers have entered a new phase in which chlorofluorocarbons have been joined by so-called environmentally friendly propellants as a means of aerosol propulsion. Active emission dry powder inhalers have been manufactured, and may supersede those based on the passive inspiratory flow of the patient. Self-contained, hand-held, aqueous spray systems are being introduced and are capable of competing with metered-dose inhalers and dry powder inhalers. The current status of pharmaceutical inhalation aerosol technology indicates a bright future for drug delivery to the lungs, not only as the site of action but also as a route of administration.

The development of the first pressurized metered-dose inhaler (pMDI) for asthma therapy (Riker Laboratories, 1956) was a major advance in the use of aerosols for drug delivery to the lungs (1). Chlorofluorocarbon (CFC) propellants were used to disperse drug particles or droplets from the inhalers in sizes suitable for lung deposition. The metering of nominal drug dose by a novel valve developed by Meshberg was central to the success of this device (2). Currently, the pMDI is the most frequently prescribed inhaler for the treatment of asthma. However, it is under increasing scrutiny because of the postulated contribution of CFCs to ozone depletion and global warming (3). Reformulation using so-called ozone-friendly propellants is the only alternative approach based on retaining pMDI technology. In response to the limited number of safe CFC propellants and reformulation opportunities, alternative devices to the pMDI have been given greater consideration. A number of research reports and patents describing the performance of dry powder inhalers (DPIs) indicate their leading position as a truly alternative technology. Conventional nebulizers are effective devices in terms of droplet dispersion and delivery to the peripheral regions of the lung, but they are not as portable as the other systems described above and are not popular for use outside the home or hospital. However, formulators are developing a new generation of hand-held, portable devices that will extend the use of aqueous aerosols as an alternative to pMDIs and DPIs.

In the 40 years since the development of the first pressurized packaged MDIs, the possibility of using the lung as a target route of administration for medicines has increased dramatically. The pages of *Pharmaceutical Technology* have often

Anthony J. Hickey, PhD, *is an associate professor, and* **Craig A. Dunbar, PhD,** *is a post-doctoral fellow in the Dispersed Systems Laboratory, School of Pharmacy, Beard Hall CB# 7360, University of North Carolina, Chapel Hill, NC 27599, tel. (919) 962-0223, fax (919) 966-6919, e-mail (AHICKEY@UNC.EDU). Dr. Hickey is a member of the Editorial Advisory Board of* Pharmaceutical Technology.

*To whom all correspondence should be addressed.

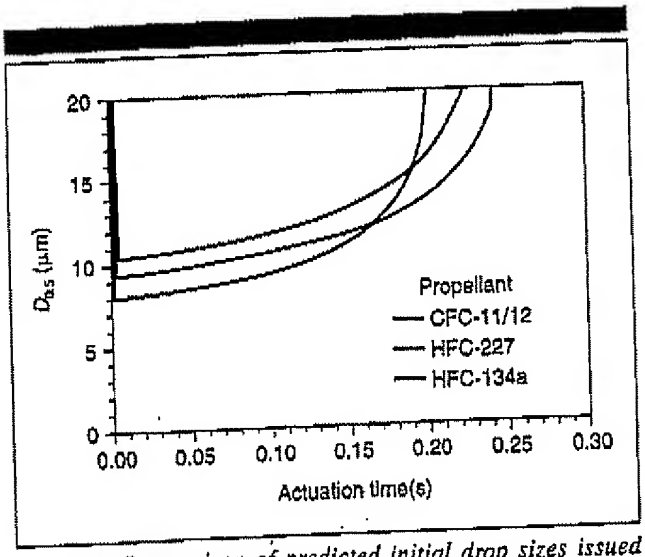


Figure 1: *Comparison of predicted initial drop sizes issued from a pMDI for various propellants.*

flected the state of the art or current debates regarding the means of delivery and characterization of these systems. The following overview addresses the role of various devices in the treatment of respiratory diseases and considers their future contributions to drug delivery to and via the respiratory tract. Methods of particle-size characterization are presented as this has been a topic of some debate in the past decade.

PRESSURIZED METERED-DOSE INHALERS

The pressurized metered-dose inhaler offers the most convenient, versatile, and cost-effective means of aerosol drug delivery available commercially. The device typically discharges more than 200 doses, producing a respirable spray of finely dispersed drug. The primary component of the pMDI is the formulation, the other components being the metering valve, actuator, and container.

The formulation most frequently consists of micronized drug particles suspended in a combination of propellants. Solution formulations are also available, but they represent a small proportion of the pressure-packaged aerosol market. Propellant blends have traditionally been a combination of chlorofluorocarbons (CFC-12, 11, and 114) providing the energy for atomization by virtue of their vapor pressure and leading to the production of respirable droplets. These propellants also have the important pharmaceutical characteristics of low toxicity, chemical stability, low cost, and good organoleptic properties.

Molina and Rowland first suggested in 1974 that the decomposition of CFCs by ultraviolet radiation in the upper atmosphere could lead to a build-up of chlorine and subsequent depletion of stratospheric ozone by the formation of chlorine monoxide (4). This was confirmed in 1985 with the discovery of an ozone hole in the atmosphere above Antarctica (5). The Montreal Protocol initiated international agreement leading to a ban on the production of all CFCs from the beginning of 1995 (6,7). As part of the effort to prevent further ozone depletion, the pharmaceutical industry responded by attempting to rapidly reformulate their pMDI devices with environmentally friendly propellants. It is not yet clear that all pMDI formulations can be reformulated in alternative propellants. Intermediate solutions the reformulation problems have been suggested (8,9). Consequently, CFC propellants are expected to be retained for delivery of some compounds for the foreseeable future.

Open discussions of the reformulation issues for pMDIs propellant manufacturers, the pharmaceutical industry, and a demicians were a prelude to an "essential use" exemption recognition of the complexities of reformulation (10,11). T situation will be reviewed in the near future, depending on t successful reformulation of pMDI products and the necessa approval by regulatory authorities. Formulation of albuterol an alternative propellant (Airomir; 3M Pharmaceuticals, Paul, MN), currently marketed in the European Union a United States, may well have a direct impact on the future CFC propellant–based products.

The alternative propellant candidates that have been asses for toxicological approval are hydrofluorocarbons (HFCs) 13 and 227. The use of alternative propellants depends upon th ability to disperse droplets or particles in similar or smaller siz than are generated by the current CFC products. Figure 1 sho the predicted mass median diameters ($D_{0.5}$) produced at the e of the pMDI actuator for each prospective alternative propel lant using an actuator flow model (12). These results are co pared with the drop sizes produced by a traditional CFC-11/1 (28:72% w/w) propellant combination delivered via a 63-μ DF60 metering valve (Perfect Valois, Greenwich, CT). The re sults predict that the alternative propellants produce small initial drop sizes than do the CFC-based propellants and there fore can be considered as suitable replacements. Reformulat of pMDIs has required modification of metering valve des and development of new surfactants and cosolvents. As the technical difficulties are addressed, a number of alternative pro pellant devices will likely be available.

One of the most significant drawbacks of the pMDI has be patient coordination at the correct point in the inspiratory e fort. Pediatric and elderly patients are most susceptible to t problems of device coordination. This is now being overco with the introduction of breath-actuated devices such as t Autohaler (3M Pharmaceuticals, St Paul, MN) shown in Fig 2a. This device incorporates a diaphragm that actuates the pl at a given inspiratory pressure, thus negating the need hand–inspiration coordination by the patient. More "intelligen devices are being developed. SmartMist (Aradigm, Hayw CA), shown in Figure 2b, is a hand-held device that integr breath-actuation capabilities, a miniature pneumotachogra and microprocessor so that a drug bolus can be delivered preprogrammed point in the inhalation cycle. Such devices certainly have a role to play in future pMDI development.

DRY POWDER INHALERS

Dry powder inhalers are of increasing interest for the delive drugs to the lungs. The basis of aerosol delivery by these tems is the combination of the powder product, the met system, and the method of dispersion. The first system fo delivery of dry powder drugs in modern times was the Spi (Fisons, Rochester, NY) (13). This system has a unique sion mechanism that combines rotation with vibration to erate the aerosol (14).

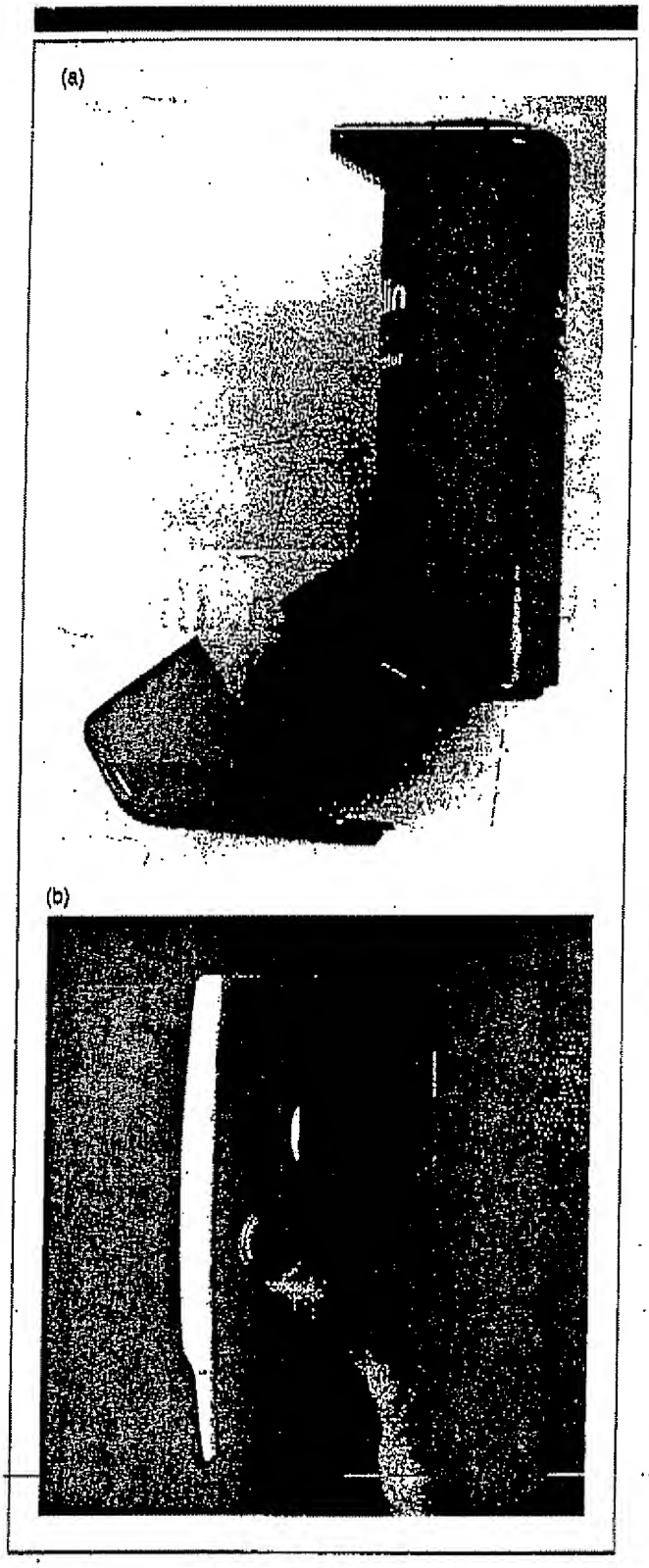


Figure 2: *Examples of breath-actuated and microprocessor-controlled pMDI devices: (a) Autohaler (3M Pharmaceuticals) and (b) SmartMist (Aradigm).*

In general, the powder product may consist of drug alone or blended with excipient (e.g., lactose). The excipient acts as a carrier with a size range of 30–60 μm, which is much larger than that required (≤5 μm) for delivery to the lung (15). These carrier particles aid in the dispersion of the drug. The ease of dispersion of drug particles relates to their particle size and tribution, morphology, and surface characteristics. These are related to the forces of interaction between particles (1 number of studies of basic powder properties and turbulent have been performed (17,18). However, further investiga may also be required for dry powder inhalers to fulfill the tential as alternatives to the pMDI (19).

The metering systems used in DPIs include hard gelati sule unit doses (Spincaps, Fisons, Rochester, NY, and Rota Glaxo Wellcome, Research Triangle Park, NC); blister aged multiple unit doses (Diskhaler; Glaxo Wellcome, Rese Triangle Park, NC) and reservoir systems (Turbuhaler; A Lund, Sweden). The stability of the powder in these syst must be considered during the formulation process. Moi ingress is a major source of both physical and chemical i bility (20). It is often necessary to include desiccants to re water from the immediate environment of the powdered d

The method of dispersion of commercially available pro is passive inhalation (Spinhaler, Rotahaler, Diskhaler, and cus; Glaxo Wellcome, Research Triangle Park, NC, and buhaler and Inhalator; Boehringer Ingelheim, Ridgefield, This has the advantage of the drug source being dispersed b patients' own inspiratory effort; its disadvantage is requiring patient's optimum inhalation flow rate to effectively disperse powder (21). Products currently under development use a dispersion mechanisms, for example, Spiros (Dura, San Di CA) and the Inhale Deep Pulmonary Drug Delivery System hale, Palo Alto, CA). These devices are shown in Figures 3a 3b, respectively. They offer the advantage that aerosol ge tion is independent of the patient's inspiratory flow. Thus, mal lung deposition and therapeutic effect are achieved.

Pharmaceutical dry powders for lung delivery are comm manufactured by jet milling and spray drying. Jet milling duces the size of particles by attrition using high-velocity posing air jets (22). Spray drying produces a dry powder by controlled evaporation of an atomized solution (23). Each these manufacturing techniques produces particles with di ent characteristics that can alter the dispersion properties o bulk powder.

A current area of interest in the production of respirable ticles is supercritical fluid manufacture. This is a contro crystallization technique in which the supercritical fluid ca presented as either a solvent or antisolvent (23–29). The vantage of supercritical fluid manufacture in the productio pharmaceutical powders is the elimination of the high-en processes (attrition and heat transfer) that might damag product (e.g., by denaturation of proteins or other labile cules). This technique is known to produce particles of uni size and morphology, which are attractive characteristic aerosol delivery.

NEBULIZERS

Nebulizers offer the simplest and most effective mea droplet delivery to the peripheral regions of the lung. The ciples used in nebulization of aqueous droplets fall int categories: airblast and ultrasonic aerosol generation. A nebulizers work on the principle that a high-pressure air produces a local pressure drop, thus drawing the fluid in

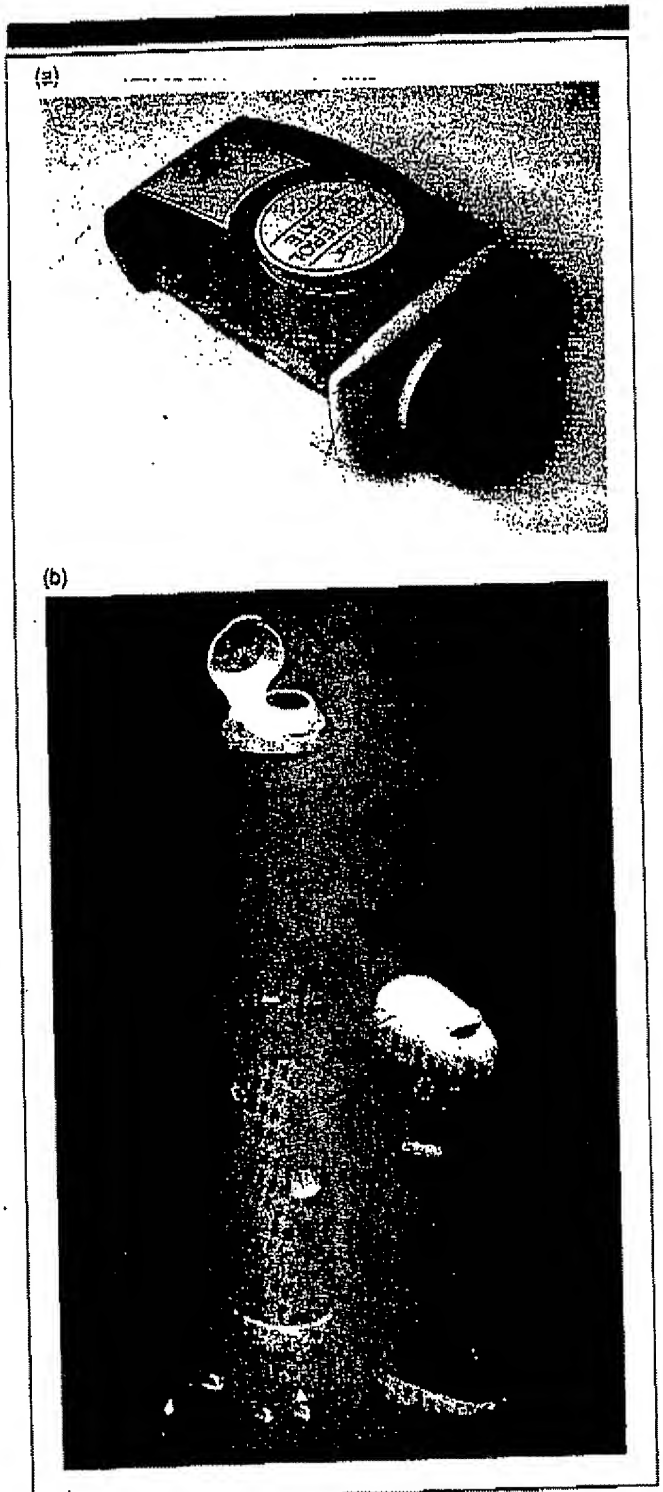


Figure 3: *Examples of active dispersion DPI devices: (a) Spiros (Dura) and (b) Inhale deep pulmonary drug delivery system (Inhale).* US 5740794

airstream by capillary action. The fine liquid stream is then disintegrated by shear forces. Ultrasonic nebulizers work by imposing a rapidly oscillating waveform onto a liquid film via an electromechanical vibrating surface. At a given amplitude the waveform becomes unstable, disintegrating the liquid film and producing small droplets.

An advantage of the nebulizer is the relative ease of formulating aqueous solutions. In the past, the principal drawback of the nebulizer was its lack of mobility because it required a compressed gas source (airblast) or electrical power unit (ultrasonic). A convenient and portable vibrating aperture nebulizer that uses a small electrical power unit (shown in Figure 4) is currently under development (Aerogen, Santa Clara, CA). This may be the first step toward a new generation of nebulizers.

One exciting prospect that has been in development during the past 5 years is that of a truly portable, hand-held nebulizer that will deliver aqueous solutions complementing the powder and pressure-packaged devices. Two new systems, the BiNeb (Boehringer Ingelheim, Ingelheim am Rhein, Germany) and AERx (Aradigm, Hayward, CA), operate on different principles that allow a single-unit dose of drug to be administered. The BiNeb consists of a nozzle that has two coincident outlet channels (~8 μm) through which the liquid dose is accelerated, resulting in impaction of the two streams and atomization. The energy for atomization is provided by a compressed spring and metering pump (30). AERx is based on the principle of a unit-dose disposable blister pack (31). A mechanical actuator forces the liquid dose in the blister container through a multiorifice nozzle, producing an aerosol (32). A heating element is provided to control the relative humidity of the inhaled air, and it includes microprocessor-controlled delivery technology, similar to that of the SmartMist.

CHARACTERIZATION METHODS

Particle-size characterization of respirable aerosols has been the subject of much discussion because of the requirement of in vitro testing and the tendency to extrapolate data to lung deposition. Methods for characterizing inhalation aerosols are diverse. They have been reviewed by the Particle Size Subcommittee of the AAPS Aerosol Group and include impinger methods, cascade impaction, laser diffraction, time-of-flight aerosol beam spectrometry, holography, microscopy, right-angle light scattering, and phase-Doppler particle analysis (33–40).

The primary method for aerosol characterization is inertial impaction, which provides information on the aerodynamic particle size and distribution by inertial differentiation of particles. A number of pharmacopeias have adopted this method. The value of inertial impaction lies in its ability to provide information on drug content of the whole aerosol, along with particle size and distribution.

Inertial impactors provide quantitative data on device performance that are extremely useful in setting product specifications but are often interpreted in terms of the potential for lung deposition. After considerable debate, discussion continues on the legitimacy of some interpretations of impaction data. Most of this discussion focuses on selection of cutoff diameters to define the aerosol distributions, representative sampling flow rates, and sampling inlet geometries. One interesting observation is that the human throat exhibits a broad cutoff collection efficiency across a range of particle diameters (41). This is illustrated in Figure 5, which shows the retention efficiency of the throat predicted by a semiempirical model for an average inspiratory flow rate of 64.5 L/min (42). The two-stage liquid impinger follows a broad cutoff collection efficiency, as shown by the calibration curve in Figure 5 for a flow rate of 60 L/min (...) retention efficiency curve similar to the one obtained ...

mentally has been predicted using computational fluid dynamics (CFD), also shown in Figure 5 (43,44). Thus, under these defined conditions the collection efficiency of the two-stage liquid impinger could be considered similar to the deposition characteristics in the oropharynx. The concept of the head as a blunt sampling inlet is not novel, and it is possible to design impactors to approximate a predetermined deposition curve (45,46). Nevertheless, anyone interested in the lung deposition of aerosols is referred to direct studies of this phenomenon. Radioisotopes may be used to quantify lung deposition, and predictive therapeutic models have been developed (47,48).

It is essential for thorough characterization that methods must not oversimplify the description of the aerosol. The complex interactions occurring within an aerosol may require a knowledge of the particle-size distribution; location of the drug; velocity of the emitted particles or droplets; fluid flow, heat, and mass transfer rates; and plume dimensions. The uncoupling of these interactions can lead to exhaustive experimental designs, and for this reason there may well be a role for computational modeling of the aerosol to provide an insight into areas that are difficult to delineate experimentally.

Standard methods of particle-size analysis for pMDIs and DPIs are being developed (49–51). In contrast, standard testing procedures have not been specified to evaluate nebulizer performance. The nebulizer has a number of components (e.g., reservoir, outlet, tubing, and mouthpiece/face mask); therefore, the definition of a benchmark nebulizer system is required because modifications in any of these parameters can significantly alter the estimated output characteristics (52). A system of this nature should be accompanied by definitions of standard operating conditions including airflow rates, adaptors, sampling tubes, and sampling times.

CONCLUSION

Many exciting developments have taken place in the technology associated with the delivery of medicinal aerosols. The Montreal Protocol brought about an irreversible change in the approach to research and development of inhalers, directly for the pMDI and indirectly for both the DPI and nebulizers (6). Multiple issues are now being addressed to improve these delivery systems in areas that were considered satisfactory before the introduction of the Montreal Protocol. Investigations into the basic mechanisms of pMDI spray production, the development of new technologies, and approaches to device development are now taking the propellant-driven inhaler into the 21st century (53–55). The same is true of the DPI, as the mechanisms of powder dispersion are better understood (14,16), along with the development of more exotic formulations and novel devices. Nebulizers will have a role to play in the future as technology transforms the device into a compact, self-contained aerosol delivery device.

New devices may be designed to satisfy patients' needs. Feedback into the design process with regard to the practical and esthetic aspects of the inhalers may become commonplace, thus making them simple to use, and capable of monitoring and modifying therapy by collating information on usage (e.g., counters, pulmonary function testing, etc.) (56). Aerosol formulations containing proteins, peptides, and nucleic acids for local and systemic therapy are already under development in parallel with novel devices for their delivery (57). However, significant challenges need to be overcome in this area, including formulation development to establish a general understanding of the complex interactions of proteins and peptides with propellants and additives, as well as degradation during manufacture, storage, and delivery (58).

Pharmaceutical Technology has always been an open forum for presentation of current and novel concepts in aerosol delivery. It will continue to be a useful medium through which to

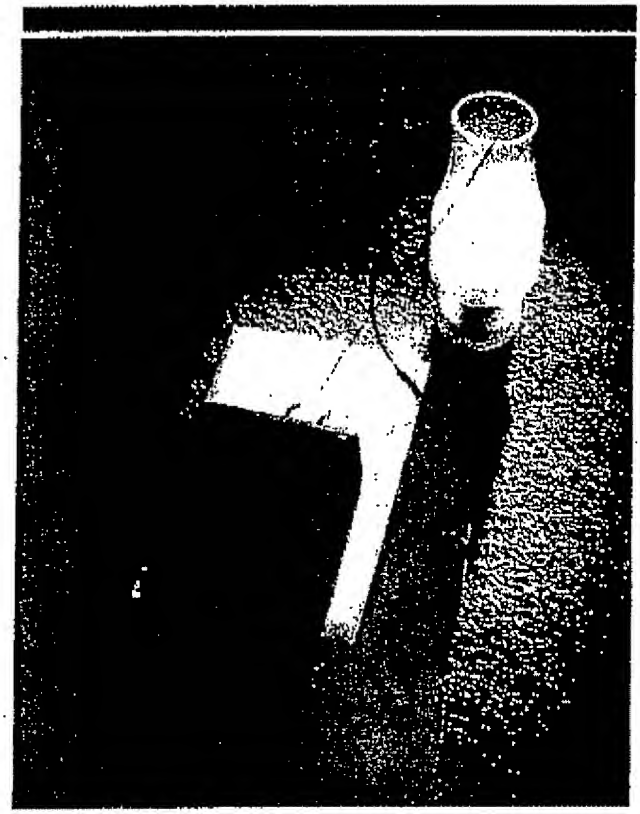


Figure 4: *Aerogen portable nebulizer (Aerogen).*

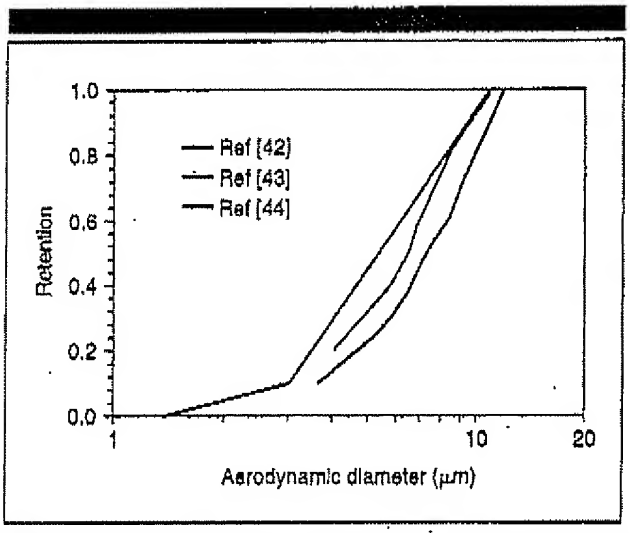


Figure 5: *Retention efficiency curves for the two-stage liquid impinger and predicted oropharyngeal deposition (42–44).*

encourage discussion and communicate information to the pharmaceutical community on new developments in the field of inhalation aerosol technology.

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NEWS BRIEF

Pump efficiency video available from DOE

The US Department of Energy (DOE) and the Hydraulic Institute (HI), a trade association of pump manufacturers, have created an educational video to promote energy efficiency in electrically powered pumping systems.

According to DOE, pumps and pumping systems account for more than 5% of the total energy used in the United States. The savings potential based on educating and training pump users and engineering contractors in the selection and use of pumps is estimated at 20%.

The video identifies specific opportunities for energy savings and explains the calculations and adjustments necessary to achieve higher efficiency. The hour-long program provides information regarding pump systems design, evaluation of performance characteristics, avoidance of excessive capacity and total head margins, and the use of multiple pumps and recovery turbines.

Production of the video was funded by DOE's Motor Challenge Program, an industry and government partnership designed to help industry save 5 billion kWh of electricity annually by 2000. The Motor Challenge promotes industrial energy efficiency through the use of efficient electric motors, drives, and driven equipment, and effective electric motor-driven system integration and optimization.

For further information on the DOE/HI video program, the Motor Challenge program, or to obtain the pump efficiency video and materials, contact the Motor Challenge Clearinghouse at 1301 Clay St., Oakland, CA 94612, tel. (800) 862-2086.